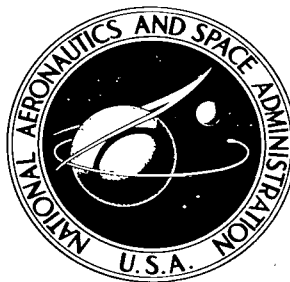
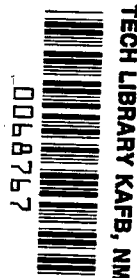


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RESTORATION OF CONTRACTILITY AND PROSPECTS FOR TRANSPLANTATION OF HUMAN AND ANIMAL HEARTS

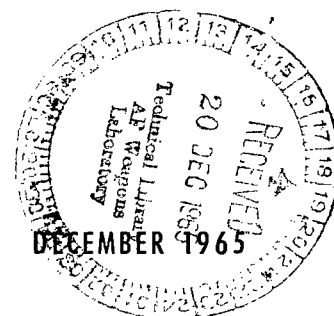
by *S. V. Andreyev*

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RESTORATION OF CONTRACTILITY AND PROSPECTS FOR
TRANSPLANTATION OF HUMAN AND ANIMAL HEARTS

By S. V. Andreyev
December 1965

Cover page and title page: Source should be Eksperimental'naya Khirurgiya i Anesteziologiya, Vol. 9 instead of Eksperimental'naya Khirurgiya, Vol. 8. The rest of the citation is correct.

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18 May 1966
S.A.V.



RESTORATION OF CONTRACTILITY AND PROSPECTS FOR
TRANSPLANTATION OF HUMAN AND ANIMAL HEARTS

By S. V. Andreyev

Translation of "O vosstanovlenii sokratitel'noy aktivnosti i
perspektivakh transplantatsii serdtsa cheloveka i zhivotnykh."
Eksperimental'naya Khirurgiya, Vol. 8, No. 4, pp. 32-36, 1964.

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RESTORATION OF CONTRACTILITY AND PROSPECTS FOR
TRANSPLANTATION OF HUMAN AND ANIMAL HEARTS

**/32

S.V.Andreyev*

Experiments on the restoration of contractility of the human heart after death and the possible resumption of hemodynamics in the organism are reported, based on postmortem examinations of 397 human hearts. The bioelectric activity of the myocardium and the significance of macroergic compounds (ortho- and pyrophosphoric acids, lactic acid, creatine, arginine, etc.) for the myocardial metabolism were studied, to obtain data on the possibility of transplanting human hearts. Restoration of contractility, up to 5 days after death and lasting for more than 15 days, was possible in all cases of undiseased hearts. Present obstacles to human heart transplantation (such as tissue or protein incompatibility, difficulty in rapid re-innervation, etc.) are discussed briefly, and prospects for future transplantations are based on successful biosynthesis of protein molecules and polymers, including the various amino acids, to be used in constructing an artificial heart without tissue incompatibility.

During the last two decades we and our colleagues have performed a series of experimental works on the restoration of the activity of the human heart after death, to elucidate a number of urgent topical problems.

In investigating the functional state of the human myocardium and its ability to resume contractile activity at various ages, upon death from infectious and somatic disease, we studied the contractility of the hearts of embryos, newborn infants, children, young people, adults, and elderly people who had died from severe dyspepsia, dysentery, diphtheria, scarlatina, bronchial pneumonia, sepsis, atherosclerosis, essential hypertension, cancer, serious injury to the central nervous system, the internal organs, and the bony skeleton.

At all stages of restoration of cardiac contractility, we studied the bioelectric activity of the myocardium, and also investigated the significance of several macroergic compounds on the myocardial metabolism (arginine, creatine, ortho- and pyrophosphoric acids, pyrotartaric and lactic acids, and atophan); ultraviolet spectrometric determination of adrenergic substances and optical absorption of proteins of the heart muscle in various stages of fibrillation or

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** Numbers in the margin indicate pagination in the original foreign text.

synchronous contractions were also investigated.

We studied the reactivity of the myocardium and its blood vessels in its dependence on the degree of infective intoxication, and the seriousness of the damage to the nervous and cardiovascular systems in various phases of development. We determined the quality of the restored contractility (intensity of contractions, duration of restored contractions and their effectiveness for possibly accomplishing hemodynamics in the organism). In other words, we performed a comparative determination of the character of the restored viability of the human heart in the postmortem period.

These studies helped to refine the degree and character of the influences of the pathological process on the contractile and metabolic functions of the heart muscle. From the degree and completeness of restoration of the contractions of some part of the whole heart it is possible to draw conclusions as to the functional insufficiency or full functionality of the myocardium as a result of the preceding pathological process. This might also form a basis for judging the possibility of transplanting the human heart after restoration of its function and of using it to replace a faulty organ in another organism.

The problems posed in our investigations cannot serve as a prerequisite for conclusions of this kind until a large amount of additional factual material has been collected.

We made two series of studies on 397 human hearts, as to the restoration of contractility and as to the reactivity of the heart blood vessels and of the myocardium.

We will confine our discussion to individual examples which, on the one hand, characterize the exceptionally high ability of the human heart to maintain its activity and energetics under the most varied conditions and, on the other hand, show the extreme importance of the functional features of the cardiac innervation as well as, even more so, that of the neural apparatus in the heart vessels, which might be considered as the starting mechanism for restoration of cardiac contractility.

The restored contractility of the human heart may persist for many hours. The heart reacts to the stimulation of extracardiac nerves, to changes in the /33 temperature of the surrounding medium, and to disturbances in artificial nutrition; in the myocardium the dynamics of the metabolism is converted into various biocurrents of differing character and form. To the rhythmic high-voltage oscillations of the potentials there corresponds one definite feature of the myocardial metabolism, and to the low-voltage arrhythmic oscillations, another feature. In fibrillating arrhythmia of the myocardium, the content of adenylic compounds, and perhaps also that of the arginine compounds, increases. After nutrition is interrupted, during its second death, the heart sometimes continues to contract for more than an hour, exactly as it happens after death of the whole organism. Thus the human heart, after restoration of its contractions, shows the same functional properties it had during life.

Heart of cadaver D., 18 years, death from bilateral suppurative otitis,

otogenic sepsis, pyemia, and thrombosis of the S sinus: The heart was placed in the apparatus 6 hr 36 min after death. Contractions of the right ventricle started after 7 min, followed by contractions of the left ventricle and of the whole heart. Observations of the contractions were continued for 3 hr 23 min.

Heart of cadaver I., 9 days old, death from erysipelas, septic pyemia and fibrocaceous peritonitis: The heart was placed in the apparatus 9 hr 5 min after death. Contractions of the whole heart started in 15 min, were studied for 13 hrs, and were then artificially stopped.

An example of the prolonged persistence of the contractility of the myocardium is given by the example of the heart of a premature infant 6 days old, who died of bilateral bronchopneumonia. The contractions of the whole heart were resumed 99 hr 20 min after death (more than 4 days) under the usual conditions of preservation of the cadaver. This period could have been increased, since the first contractions of the right ventricles began 20 min after the heart was placed in the apparatus, and after another half hour, contractions of the whole heart set in. The long time (50 min) required, from the time the heart was placed in the apparatus to the development of contractile activity in all its parts, is explained by the existence of a longitudinal block before the beginning of the experiment.

The activity of the human heart after death from various diseases has been restored after 43 hrs. Our experiments give us the right to state that the longest period for survival of the venous vessels of the human heart is about 5 days (111 hrs) after death. Restoration of the contractility of the myocardium is always preceded by the appearance of vasomotor activity of the heart. The latter, in the absence of cardiac contractions, is demonstrated by tonic spasm experiments and by subsequent dilatation of the coronary blood vessels.

In one of our experiments on the heart of a 58 year old male who had suffered from gastric ulcer and died from a thromboembolism of the pulmonary artery in the postoperative period (following partial resection of the stomach), a sharp vascular spasm was observed. As a result, the coronary efflux declined from 375 to 70 ml in one minute, i.e., by 81.4%.

In an experiment on the heart of a 59 year old male who had died from injury to the skull and brain, on injection of cardiophyllin ($1:5 \times 10^3$) we noted a distorted reaction of the cardiac blood vessels: the coronary blood flow decreased from 400 to 55 ml in one minute (by 86.3%).

In an experiment on the heart of a 70 year old male who had died from multiple traumatic injuries of the bones and organs of the body, we observed, in contrast, under the action of nitroglycerine, a considerable dilatation of the myocardial blood vessels, and the coronary flow increased from 130 to 276 ml in six minutes (by 212.2%).

A strong rhythmically varying vasomotor reaction sometimes takes place in the diseased heart of a corpse. In an experiment on the heart of a 56 year old male who had died during an attack of stenocardia and had a stenosed coronary atherosclerosis with thrombosis of the descending branch of the left coronary artery, the tonus of the vascular blood vessels fluctuated periodically every

1 - 4 min, causing a change of 20 - 120 ml in the coronary efflux.

The above examples (and others) indicate that the activity of the cardiac blood vessels may be autonomous and independent of the activity of the myocardium (under pathological conditions). The isolated human heart can be considered as a peculiar model of a rapidly developing spasm of the coronary blood vessels and of a "sudden" onset of cardiac insufficiency (developing within the span of a minute) and imitating an attack of stenocardia. Dilatation of the cardiac blood vessels takes several times as long (4 - 6 min). The vasomotor activity of the human heart is pronounced and has a great capacity for rhythmically ^{/34} varying the coronary flow in relatively short intervals. This is the reason for the major ability of the cardiac blood vessels to maintain not only the functions of the heart but also the hemodynamics of the organism. Such an assumption is strengthened by the great mass of the arterial and venous blood vessel of the heart and of their anastomotic branches which, taken together, apparently occupy not less than half the entire volume of the heart.

The technique of restoration of cardiac activity must be perfected, and in particular the physical work of its contraction must be emphasized, by application of various loads for this purpose.

These examples show that, in various intoxications and structural alterations of the vascular wall and the myocardium in individual cases, a complete restoration of the contractions of the cardiac musculature is possible even long after death (4 days). In other cases, however, in spite of the short time since death of the organism had taken place (from 3 to 11 hours) due to such causes as lymphosarcomatosis, pulmonary edema, or bilateral cavernous pulmonary tuberculosis, restoration of cardiac contractility is impossible. It must be assumed that intoxications or other forms of damage to the nervous system cause efferent impulsation due to the respective biochemical compounds, thus blocking the possibility of resumption of the diffusional, oxidation-reduction potential and, consequently, of the cellular metabolism.

These experiments distinctly recall the acute cardiac insufficiency observed on the operating table, when the surgeon, using modern methods of restoring cardiac contractility, is unable to overcome the force of the blocking impulses coming from the central nervous system or originating in the heart itself. We are not speaking here of the situation when, as a result of a prolonged pathological process, the reactivity of the patient is distorted and the metabolism of his nervous system is disturbed, but when, instead, the severe operative trauma to the myocardium and other parts of the organism, together with excessive pharmacodynamic effects, so complicates the already serious condition of the patient as to cause almost irreversible changes in the protein molecules. Such a situation should be the object of persistent and purposeful research by biologists, biochemists, biophysicists, pathophysiologists, and clinicians, so as to obtain a better understanding of the mechanism of its appearance and to discover preventive measures.

Experiments on the heart muscle have shown the exceptionally great importance of maintaining adequate vascular reactivity. When this reactivity is thrown out of balance, the reflex from the vascular wall under the action of a

given substance introduced into the vascular channel may cause a persistent and prolonged spasm, not only partial, but even total, of the cardiac blood vessels, which may be one of the factors leading to the development of cardiac insufficiency. This entirely real mechanism of its appearance should be taken into account not only by therapists but by heart surgeons as well.

The heart of a cadaver is not only an object for further study of its metabolism and functional features, as stated by I.P. Pavlov, but can also be used in individual cases as an object of transplantation into the organism of another human subject.

The data obtained are still insufficient for serious and promising conclusions in this direction; they are, however, of interest and do justify further investigations of the human heart. The problem of transplantation of the heart, which is of exceptional importance, must be given high priority in modern medicine. Its correct solution will require systematic and detailed study of the metabolism of the human heart muscle, which will yield a firm foundation for the realization of suitable intervention and proper control of this metabolism.

At the present state of the art, however, despite the high skill in modern surgical techniques of transplanting the heart in large animals, a transplantation of the human heart is still impossible. The following may be considered the major obstacles to the solution of this problem. /35

1. Tissue or protein incompatibility. The incompatibility of individual protein structure is a basic and more complex obstacle to the realization of organ transplantation than would be expected from only a study of the immunological peculiarities of individual human organisms. The general state of each individual, psychoneurological, structuro-neurological features, his characteristics, the fine ramifications in the structure of his particular protein molecules, whether they relate to the chemical structure of his own hormones or of the proteins forming the basis of his cutaneous and mucous membranes - all these features are extremely individual and will require an enormous amount of work to overcome them. This work is entirely promising and no doubt can be realized eventually. The sooner we are able to define the pathways of biosynthesis of the extremely complex large protein molecules, the sooner will the solution of this major scientific problem become actuality.

2. The heart, like other organs, can function correctly only in the presence of innervation connections with the rest of the organism. Cardiac activity is regulated every second by reflexes originating not only in the heart itself but in all parts of the organism. Consequently, another important problem arises. This is the problem of a rapid re-innervation of a heart transplanted into another organism. The growth of the cardiac and extracardiac nerves must be accelerated since, on transplantation of the heart, both types of nerves are damaged or partly destroyed. Work in this direction has been started, but the present level of stimulation of nerve regeneration is not yet sufficient for solving this problem.

The rapid re-innervation of a transplanted heart is necessary not only for a correct regulation of its activity and for a regulation of the hemodynamics within the organism, but primarily for ensuring myocardial metabolism. The in-

tensity and quality of the metabolism of denervated tissues and organs are extensively interfered with. The disturbance of the metabolism may also be one of the factors responsible for the subsequent death of the transplanted organ, and, together with it, of the transplantee.

The interesting animal experiments on the dog, performed by V.P. Demikhov, only confirm the above propositions.

In recent years, biophysics, chemistry, and biochemistry of polymer compounds have made tremendous progress, going beyond the boldest and most fantastic dreams of researchers, and it is therefore likely that the solution of the problem of the biosynthesis of the extremely complex protein molecules will be accompanied by the parallel solution of the problem of biosynthesis of polymer compounds in the organism, including the various amino acids. It is possible that such polymer compounds will not have the typical properties of tissue incompatibility, so that biologists, physiologists, clinicians, and technological designers will be able to construct an artificial organ (heart) possessing universal prosthetic properties, without tissue incompatibility. The studies now underway to diminish the individual protein incompatibility by the use of ionizing radiation, blood exchange, etc. must be continued and expanded, since this line of investigation does not exclude possibilities for elucidating and solving the problems on which we have touched.

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